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Pancytopenia Due to Bone Marrow Necrosis in Acute Myelogenous Leukemia: Role of Reactive CD8 Cells

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Bone marrow necrosis is a rare clinical condition often associated with hematological malignancy. The mechanism by which malignant disease causes marrow necrosis is unknown. We present a case of a patient with newly diagnosed pancytopenia with bone marrow biopsy evidence of extensive marrow necrosis. Upon further work-up utilizing Tc bone scan directed bone marrow biopsy, a massive CD8+ T cell marrow infiltrate was discovered engulfing AML-M2 blasts. The role of Tc bone scans in the work-up of bone marrow necrosis as well as the potential mechanism of AML-M2 induced marrow necrosis in the setting of reactive CD8+ T cell infiltration is discussed. Am. J. Hematol. 59:74–78, 1998. © 1998 Wiley-Liss, Inc.

Key words: bone marrow necrosis; acute myelogenous leukemia; CD8+ T cells; bone scan

INTRODUCTION

Bone marrow necrosis (BMN) is a relatively rare and unusual phenomenon of bone marrow destruction. It has been described in different series with frequencies varying between 0.5 to 37% of sequential bone marrow biopsies [1,2]. Varying degrees of BMN have been associated with multiple clinical conditions including: acute myelogenous leukemia [3], chronic myelogenous leukemia [4], acute lymphocytic leukemia [4–7], chronic lymphocytic leukemia [8], hairy cell leukemia [9], lymphoma [10,11], all-trans retinoic acid therapy [12], fludarabine [13], *Escherichia coli* sepsis [14], antiphospholipid syndrome [15,16], sickle cell disease [17], primary thrombocythemia [18], adenocarcinoma of unknown primary [19,20], Pseudomonas aerugenosa sepsis [19], mucor infection [21], idiopathic [22], and anorexia nervosa [23]. BMN is most often recognized on post mortem evaluation [11]. As a clinical syndrome, BMN has been described in cases of patients presenting with the triad of fever, bone pain, and a peripheral smear demonstrating a leukoerythroblastic reaction or pancytopenia [10]. Most often, BMN is the end result of an insult to the bone marrow either by a malignancy, massive infection, a prothrombic state, or chemotherapy [1,10,11,14,22]. The pathophysiology of BMN has been a subject of some debate. Hypotheses attempting to explain the mechanisms of BMN have included: toxic effects of prior chemotherapy [24,25], prior therapeutic irradiation [10,5,26], endotoxemia [27], widespread microvascular infarction (in sickle cell disease [28,29,30], decreased regional oxygen tension due to increased proliferative capacity of marrow infiltrating cells [10], TNF [19], and thrombosis [16].

Herein we present a case of a patient presenting with pancytopenia with a bone marrow biopsy demonstrating BMN in the setting of a newly diagnosed acute myelogenous leukemia (AML-M2) associated with a massive CD8+ T cell reaction in the bone marrow. The potential role of the CD8+ cell response is discussed.

CASE REPORT

The patient is a 70-year-old man with a 1-month history of fatigue, fevers up to 102°F, and chills. Past medical history is significant for hypertension and benign prostate hypertrophy. The patient had been complaining of progressive lack of energy and worsening pain in the right lower ribs and low back for 2 months prior to initial evaluation. Over the last several days he had started com-

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TABLE I. Admission Laboratory Results*

Test	Normal range	Patient
WBC ($\times 10^9$/L)	3.5–10.5	3.0
Hb (g/dL)	13.5–17.5	9.9
Platelets ($\times 10^9$/L)	150–450	65
MCV (fL)	81.2–95.1	82
Neutrophils ($\times 10^9$/L)	1.7–7.0	2.3
Lymphocytes ($\times 10^9$/L)	0.9–2.9	0.6
Monocytes ($\times 10^9$/L)	0.3–0.9	0.1
Basophils ($\times 10^9$/L)	0–0.1	0.0

*WBC, white blood cell; Hb, hemoglobin; MCV, mean corpuscular volume.

plaining of a new right flank discomfort. Ten days prior to transfer to our institution, the patient was hospitalized in a local hospital with fevers of 102°F. Upon that admission, the patient was found to be pancytopenic (Table I) and had a positive hemoccult exam. Work-up was initiated, trying to identify the etiology of the pancytopenia and the source of gastrointestinal blood loss. Multiple studies were conducted (serum and urine electrophoresis, CT scans of the chest, abdomen and pelvis, fungal serologies). Ultimately, a bone marrow biopsy was performed demonstrating marrow necrosis.

With the above history, the patient was transferred to a tertiary referral medical center for further evaluation and treatment. Admission laboratory studies demonstrated a persistent pancytopenia with a positive hemoccult. Repeat colonoscopy identified sigmoid diverticula that were identified as the source of bleeding. Review of the outside bone marrow Bx was performed, confirming the diagnosis of bone marrow necrosis.

With the patient's ongoing/progressive right flank pain, now more localized to the right lower ribs, a Tc-bone scan and a skeletal bone survey were performed looking for rib fractures and/or bone metastases (Fig. 1). Increased uptake on the bone scan with negative bone survey findings (no lytic lesions/blastic lesions) suggested a marrow infiltrative process, possible metastatic malignancy. In order to make a diagnosis, a biopsy of the area of largest uptake was obtained (right iliac crest).

The result of the biopsy was intriguing (Fig. 2). Adjacent to the areas of marrow necrosis, there appeared to be a massive infiltrate of atypical mononuclear cells replacing entire marrow space and in some areas extending into periosteum. Upon higher power exam the infiltrating cells appeared to resemble T cells (Fig. 3). Immunohistochemical staining confirmed that the majority of the cellular infiltrate was made up of CD3+ cells (Fig. 4).

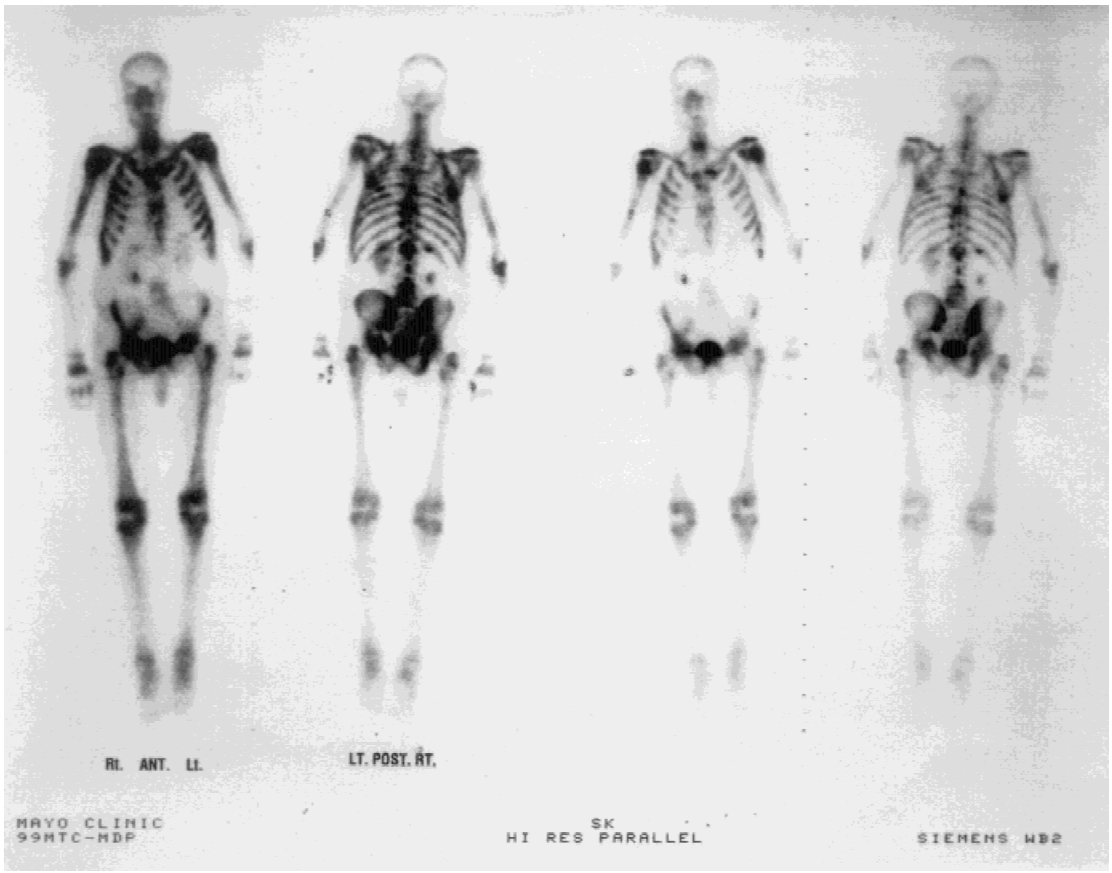

Fig. 1. Tc-bone scan demonstrating multiple areas of uptake. Highest uptake was noted in the right iliac crest.

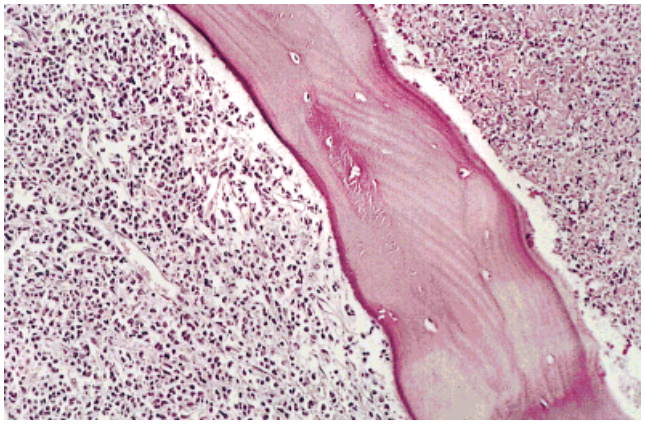

Fig. 2. Photomicrograph of a bone marrow biopsy demonstrating a bony spicule separating an area of bone marrow necrosis (right upper corner of the field) from an extensive small cell infiltrated (H&E stain, ×265).

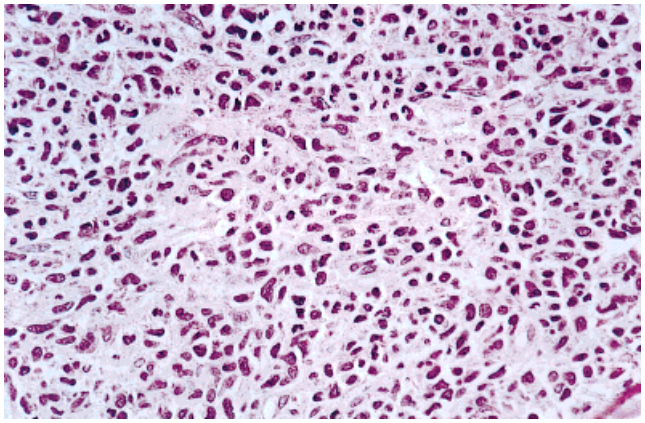

Fig. 3. Photomicrograph of a bone marrow biopsy demonstrating a higher power view of the cellular infiltrates. The morphologic appearance of the infiltrating cells is compatible with that of T cells (H&E stain, ×640).

The appearance of the T cell infiltrate was very suggestive of a primary T cell lymphoma of the bone marrow. In view of the lack of any detectable adenopathy or splenomegaly on CT scanning and the unusual bone marrow findings suggestive of a T cell lymphoma involving the bone marrow alone, a confirmatory T cell receptor gene rearrangement study was performed. Days later, unexpectedly, the T cell receptor gene rearrangement study demonstrated no evidence of a clonal T cell process involving the bone marrow. Faced with this development, further studies of the bone marrow samples were performed, including a myeloperoxidase stain (Fig. 5). Interspersed between the invading T cells were AML-M2 leukemic blasts suggesting the diagnosis of AML. In order to gain some understanding of the massive T cell infiltrate encasing the AML blasts, a CD8 immunohistochemical stain was performed (Fig. 6). It appeared that the phenotype of the majority of the CD3+ infiltrating T

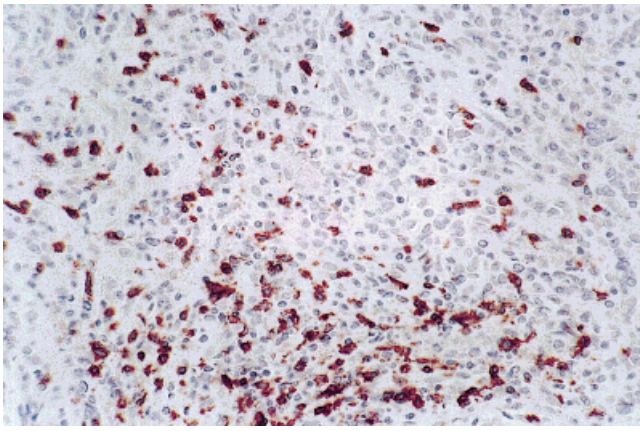

Fig. 4. Photomicrograph of a bone marrow biopsy demonstrating that most of small infiltrating cells are CD3 positive T cells (immunoperoxidase stain for CD3, ×640).

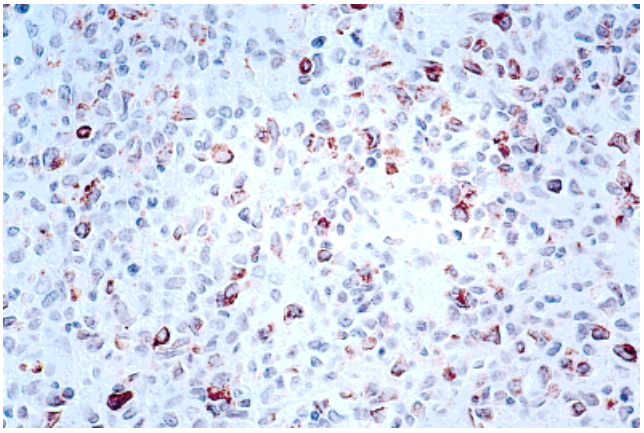

Fig. 5. Photomicrograph of a bone marrow biopsy demonstrating many myeloperoxidase positive myoblasts interspaced between the infiltrating T cells.

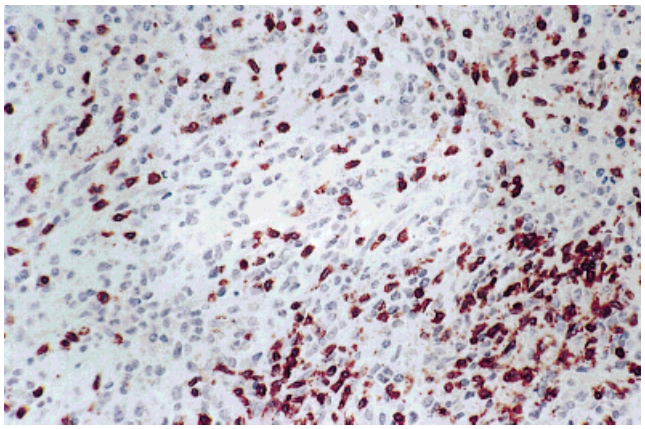

Fig. 6. Photomicrograph of a bone marrow biopsy demonstrating that the majority of infiltrating T cells are CD8 positive cytotoxic/suppressor cells (immunoperoxidase stain for CD8, ×640).

cells was CD8+ as well, suggesting that the invading T cells were T cytotoxic/suppressor cells, i.e., the effector arm of the T cell immune response.

DISCUSSION

BMN has been described in multiple clinical scenarios, with the diagnosis made mostly at autopsy. The reason for this is the relatively low frequency of the phenomenon (pre and postmortem), the multitude of disease processes associated with BMN, as well as the lack of more specific clinical clues for this diagnosis [1,4,10,11,22,31,32]. The presented case suggests several important points. First, in dealing with BMN in a patient with worsening symptoms, a bone scan can be helpful in detecting viable tissue in the bone marrow, a biopsy of which could be diagnostically useful. Second, although the morphologic features of the marrow biopsy were very suggestive of a T cell lymphoma, the genetic analysis of the sample demonstrated lack of a clonal T cell population. This prompted a re-evaluation of the original marrow to look for causes of a massive polyclonal T cell immune response (neoplastic or infectious), ultimately leading to the correct diagnosis of AML. This illustrated the utility of the T cell receptor gene rearrangement study in such cases. Third, this case is the first example of a massive T cell immune response in the bone marrow triggered by a subclinical AML (no peripheral blasts). The predominantly CD8+ T cell infiltrate engulfing the AML blasts in immediate proximity to areas of extensive marrow necrosis suggests the possibility that the T cells themselves may be responsible for the necrosis of the marrow. Not unlike the setting of other autoimmune/viral diseases where the immune response to the offending agent is the cause of tissue injury, it is possible that the massive cytokine release from this exaggerated T suppressor/cytotoxic lymphocyte infiltrate may be reacting to leukemic cells and also destroying ''innocent bystander'' bone marrow elements, resulting in BMN with presenting pancytopenia, long before AML became manifest in the peripheral blood. It has already been suggested that some patients with BMN have an increased TNF serum level [19]. This monokine may indeed play a central chemoattractant role for the invading T cells rather then directly causing marrow necrosis. Unfortunately, we were unable to obtain serum TNF levels in this case.

CONCLUSION

The present case illustrates the difficulties in defining the underlying cause of pancytopenia in the setting of BMN. It also demonstrates the unusual presentation of AML-M2 as BMN and pancytopenia. It is our impression that the use of a Tc bone scan rather than a Tc sulfur-colloid marrow scan as a guide for bone marrow biopsies is more useful in the workup of BMN because it will identify rapidly proliferating cells in the necrotic marrow and, therefore, aid in diagnosis. The sulfur colloid scan is taken up largely by bone marrow elements and may only identify areas of viable marrow not involved in the disease process.

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